Remarks

Claims 21-24 and 29-30 have been amended, and claims 31-48 have been added, to more particularly point and distinctly claim that which Applicants believe to be the invention. With this amendment, claims 21-24 and 29-48 are pending in this application.

Claim 21 has been amended to recite a method for enhancing a human antigen presenting cell (APC)-mediated human cytotoxic T lymphocyte (CTL) response, comprising stimulating an APC with an agonist anti-CD40 antibody, or binding fragment thereof, wherein said anti-CD40 antibody or binding fragment is capable of blocking binding of CD40L on a human T lymphocyte to CD40 on a human APC by 16-88% and wherein said antibody synergistically enhances APC-mediated human CTL activation. Support for claim 21 as amended can be found in the specification at, *e.g.*, page 1, lines 3-5; page 2, lines 5-24; page 3, line 28 to page 4, line 1; page 4, lines 10-15; page 6, lines 7-16; page 18, line 26 to page 19, line 8; page 20, lines 5-11; page 21, lines 3-26; page 22, lines 19-20; page 24, lines 1-4; and Figures 1, 2, 3, and 5.

Claims 22-23 and 29-30 have been amended to depend from new claim 31. Claim 24 has been amended to depend from new claims 31 and 32, and to recite an antibody in which potential T cell epitopes have been eliminated. Support for this amendment to claim 24 can be found in the specification at page 8, lines 10-11.

New claim 31 recites a method for enhancing an antigen-specific cytotoxic T cell (CTL) response, wherein said CTL is activated with a human antigen presenting cell (APC) and wherein said APC is stimulated via the CD40 receptor with an antibody or binding fragment thereof that binds to said receptor and blocks binding of CD40L to CD40 by 16-88%. Support for claim 31 can be found in claim 21 as filed, and as described for amended claim 21, above. New claim 32 recites the method of claim 31, wherein CD40-CD40L binding is blocked by 16-88%. Support for claim 32 is found on page 22, lines 19-20.

New claims 33-48 recite the monoclonal antibodies of the invention, or fragments thereof, and the hybridomas that produce these antibodies, according to the accession numbers established for each hybridoma as deposited with the American Type Culture Collection (ATCC).

The hybridomas were generated and tested by the methods of the invention as described in Examples 1-6 of the specification. The hybridomas correspond to the clones as cited in the specification at page 5, line 10, and in Figures 1A-5B, as follows, in relation to the hybridoma depositor reference and ATCC deposit accession numbers: clone 4 (hybridoma MAb 186-4-1, ATCC Accession No. PTA-2996), clone 7 (hybridoma MAb 186-7-2, ATCC Accession No. PTA-2997), clone 15 (hybridoma MAb 186-15-1, ATCC Accession No. PTA-2998), clone 21 (hybridoma MAb 186-21-1, ATCC Accession No. PTA-2993), clone 26 (hybridoma MAb 186-26-3, ATCC Accession No. PTA-2999), clone 64 (hybridoma MAb 186-64-1, ATCC Accession No. PTA-2994), clone 70 (hybridoma MAb 186-70-3, ATCC Accession No. PTA-2995).

The specification has been amended to recite the ATCC deposit information for these hybridomas as recited above. Applicants submit herewith Exhibit A, a copy of the ATCC receipt of deposit of the listed hybridomas under the provisions of the Budapest Treaty. Applicants bring to the Examiner's attention the date of deposit of the hybridomas with the ATCC on January 31, 2001, prior to the filing date of the instant application on February 1, 2001. As these hybridoma clones are provided in the specification and figures as filed (see the specification at page 5, line 10, and Figures 1A-5B), Applicants submit that amendment of the specification and addition of new claims 33-48 do not constitute new matter. Manual of Patent Examining Procedure (MPEP) 2406.01.

No new matter has been introduced in these amendments. Upon entry of these amendments, claims 21-24 and 29-48 will be pending. Entry and consideration of these amendments is respectfully requested.

Applicants note with appreciation that the replacement drawings submitted April 27, 2005 have been accepted by the Examiner.

Rejection under 35 U.S.C. § 112, second paragraph, indefiniteness

The Examiner has rejected claim 24 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner

argues that the trade name "DeImmunized™" is indefinite, because the trade name identifies the source of the product and not the product itself.

In response, claim 24 has been amended to delete the reference to "DeImmmunized™" and instead claim the use of antibodies "in which the potential T cell epitopes have been eliminated." This amendment is supported in the specification. Applicants therefore respectfully submit that the rejection under the second paragraph of 35 U.S.C. § 112 has been obviated, and should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph, written description

The Examiner has rejected claims 21-24 and 29-30 under 35 U.S.C. § 112, first paragraph, for alleged lack of written description. The Examiner alleges that the specification as filed does not provide support for the terms "for enhancing a pre-existing immune response", "contacting", and "without completely blocking" in the claims as amended. The Examiner rejects these limitations as new matter and insists that the terms be canceled.

Applicants submit that these terms are inherently if not expressly taught in the specification as filed. However, in order to further prosecution of this application, claim 21 has been amended to remove these terms. Further, new claim 31, which has literal basis in the specification as outlined above, has been added. Applicants submit that the cancellation of the terms of claim 21 as requested by the Examiner obviates the rejection for lack of written description and request that the rejection be removed.

Rejection under 35 U.S.C. § 112, first paragraph, enablement

The Examiner has rejected claims 21-24 and 29-30 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner alleges that *in vitro* and animal model studies do not correlate well with *in vivo* clinical trial results in patients. The Examiner argues that, in the absence of *in vivo* clinical data, it would be too unpredictable to determine the efficacy of a therapeutic strategy, and that the specification does not enable a person of ordinary skill in the art to practice the invention.

Applicants respond that the claims of the application are properly enabled for the methods of enhancing an APC-mediated CTL response with the use of anti-CD40 antibodies, in the absence of administration of antigen, for the following reasons.

Applicants submit that co-administration of antigen is not a prerequisite to the treatment of compromised immune function. Human disease states can involve an antigen against which an immune response may be mounted, but mounted only poorly. For example, an immunocompromised individual may need assistance in mounting a normal immune response to a pathogen against which a healthy individual would easily mount a response. In this case, immunogenic antigens are in the individual's system, but the immunocompromised patient may require a "boost" to properly activate the immune system. The agonistic anti-CD40 antibodies of the invention would enhance a weak CTL response mounted by the patient against the pathogen. Administration of antigen would not be necessary to utilize the methods of the claims. The specification discloses that key elements of an immune response can be initiated in the absence of antigen administration, as evidenced by maturation and stimulation of dendritic cells by application of the CD40 antibodies of the invention in the experiments disclosed in Example 3, pages 19-21.

As a further example, T cells specific for tumor antigens can be isolated from patients with tumors, indicating an existing recognition of the antigen or antigens by the immune system. However, this antigen recognition may require a "boost" in order to be effective. As the antigen or antigens are already present, there is no need to provide further antigen. What is required is additional activation of the CTL response. Such an enhancement is provided by the methods of the invention. Enhancement of the CTL response to already present antigen is achieved by stimulating APCs via the CD40 receptor with an agonistic antibody of the invention, which in turn activate CTLs to respond to the tumor antigen or antigens. One of skill in the art, seeking a method to enhance the immune response to an antigen in the system of a patient, would immediately grasp the significance of the claimed methods, and would be able to utilize the methods as taught in the specification, without the need to administer antigen to the patient.

The Examiner emphasizes providing an antigen-specific response. However, Applicants respectfully point out that the claimed methods are not directed toward providing a response to a specific administered antigen, but rather are directed toward enhancing a response to an antigen which may already be present in the system of the individual. In the examples provided above, a response against any of the antigens to be fought would be desired, so to artificially provide only a single antigen, or even a subset of antigens, would not be as effective as enhancing the response to the sum of foreign antigens already present in the individual.

In addition, Applicants note that antigen uptake by APCs is a separate event from APC stimulation and interaction of APCs with T cells. As described in the specification's background of the invention, APCs take up antigen at sites of antigen introduction and circulate to the lymph nodes, where they present antigen to T cells. Stimulation of APCs and enhancement of the APC-T cell interaction, therefore, does not happen simultaneously with antigen uptake. By this reasoning, there is no clear advantage nor need to co-administer antigen along with the anti-CD40 antibodies of the methods as claimed. The methods of the claims treat the events of APC stimulation and enhancement of CTL response. It is not essential that the methods further provide for presentation of antigen for uptake by APCs; therefore, the specification need not enable this step as it is not necessary to practice the invention and enhance an APC-mediated CTL response.

The Examiner further contends that pharmaceutical therapies in the absence of *in vivo* data are unpredictable. In response, Applicants remind the Examiner that, as stated in the MPEP chapter 2164.02, an *in vitro* model example in the specification constitutes a "working example" if that example "correlates" with a claimed method. Further, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Here, Applicants have provided a recognized model system for studying immune system function. The animal cell model described in the specification is a well-recognized system in the art; thus, the results derived from this model system should be accepted by the Examiner as by one of skill in the art. As such, the examples provided by the Applicants must be accepted as a working model for the claimed methods for enhancing an APC-mediated CTL response.

The Examiner points to experiments in Melief et al. (US 2003/0022860) where mice injected with agonistic anti-CD40 antibody in combination with E1A vaccine produced strong E1A-specific CTL response while mice injected with only vaccine or antibody did not.

In response, Applicants submit that the experimental results in Melief are most relevant to the Melief invention and merely underline the highly controlled nature of Melief's experimental procedure. In order to show that the mice of Melief's experiments can mount an enhanced response to a specific antigen, the mice must be exposed to the antigen to be tested against. In contrast, the claimed methods relate to enhancing an immune response to any foreign antigen in an individual's system. Therefore, the methods of the present invention are enabled to the skilled artisan, because an artisan seeking to enhance an immune response in an individual need not determine the antigen to which an immune response is to be mounted to practice the methods as claimed. Instead, the artisan can simply apply the agonist anti-CD40 antibodies of the invention as taught in the specification.

The use of antibodies as pharmaceutical therapies is well known in the art. The methods of the invention have been demonstrated, as noted, in an *in vitro* system that is accepted in the art as a model for studying immune response. Therefore, the specification is enabling to those of skill in the art to make and use this method for enhancing an immune response in the absence of administered antigen.

Rejection under 35 U.S.C. § 102(e)

The Examiner has rejected claims 21-24 and 30 under 35 U.S.C. § 102(e) as allegedly anticipated by Melief *et al.* (US 2003/0022860) ("Melief"). The Examiner argues that Melief teaches the use of agonistic anti-CD40 antibodies for enhancing immune responses.

Anticipation requires that each and every element of the rejected claim(s) be disclosed in a single prior art reference. See MPEP 2131 (8th Ed. Rev. 2, May 2004). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d

628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Every element of the claimed invention must literally be present, arranged as in the claim. *Perkin Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 894, 221 USPQ 669, 673 (Fed. Cir. 1984).

Applicants respond that Melief fails to teach all of the limitations of the present invention.

Applicants submit that the agonist antibody disclosed in Melief differs substantially, and thus does not anticipate, the antibodies or uses thereof of the claims presented herein.

Applicants submit that the agonist antibody disclosed in Melief is unrelated to the antibodies of the instant invention, in type, in species cross-reactivity, and in function. Melief describes the use of FGK45, a *rat anti-mouse* monoclonal antibody (see www.alexis-corp.com/apoptosis-ALX-805-046/opfa.1.1.ALX-805-046.1.4.1.html, attached as Exhibit B). FGK45 is a rat antibody that recognizes *mouse* CD40. In contrast, the instant application provides *mouse anti-human* monoclonal antibodies, which are mouse antibodies that recognize *human* CD40.

The agonist antibody disclosed in Melief is also functionally distinct from the antibodies of the present claims. The antibodies of the claims activate CD40 in addition to blocking CD40-CD40L interaction by 16-88% (see the specification at page 18, line 26 to page 19, line 3, and page 22, lines 19-20). In contrast, FGK45 activates CD40 but does not block CD40 binding to CD40L, much less block binding of CD40 to CD40L by 16-88% as claimed. Applicants note that in Melief's experiments in which blockade of CD40-CD40L was desired, the CD40L-blocking antibody MR1—which does not agonize CD40—is utilized (see, e.g., Melief at Example 2). As FGK45 does not block binding, much less by a specified percentage, Applicants submit that the antibodies of the invention cannot be anticipated by any reference to it. Thus, the antibodies and methods of the invention are not anticipated by Melief's disclosure of FGK45.

The antibodies disclosed in Melief do not anticipate the antibodies of the present claims. Melief does not disclose an agonist antibody directed against human CD40 that blocks binding of CD40 to CD40L by 16-88%. Accordingly, Melief does not teach every element of the claims as

amended, and cannot anticipate the present invention. Therefore, Applicants submit that the claims are not anticipated by Melief, and respectfully request that the rejection under 35 U.S.C. § 102(e) be withdrawn.

Rejections under 35 U.S.C. § 103(a)

The Examiner has rejected claims 21-24 and 30 under 35 U.S.C. § 103(a) as allegedly obvious over Melief in view of Zhou *et al.* (Hybridoma 1999, 18:471-488) ("Zhou") and/or Caux *et al.* (*Research in Immunology* 1994, 145:235-239) ("Caux") and/or Katira *et al.* (Leukocyte Typing V, Schlossman *et al.*, Ed.) ("Katira") and/or Schwabe *et al.* (*Hybridoma* 1997, 16:217-226) ("Schwabe"). The Examiner alleges that Melief teaches methods of treating tumors or infectious diseases comprising adminstering anti-CD40 antibodies or fragments to generate or enhance immune responses. In particular, the Examiner argues that Melief discloses the anti-CD40 antibody FGK45, and that the remaining references teach that a number of agonistic anti-CD40 antibodies were well-known in the art. The Examiner alleges that it would be obvious to combine the teachings of Melief and, for example, Schwabe, to reach the present invention.

The Examiner has also rejected claim 29 under 35 U.S.C. § 103(a) as allegedly obvious over Melief in view of Zhou and/or Caux and/or Katira and/or Schwabe as applied above, and further in view of Maraskovsky *et al.* (U.S. Patent No. 6,497,876) ("Maraskovsky"). The Examiner alleges that Maraskovsky teaches the missing limitation of the use of interferon-γ to treat tumors and infections. The Examiner argues that it would be obvious to combine the teachings of these references to reach the present invention.

To establish a *prima facie* case of obviousness, the Examiner must meet three criteria. The Examiner must establish that (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations. See MPEP 706.02(j) and 2143. The teaching or suggestion to make the claimed combination and the

reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q2d 1438 (Fed. Cir. 1991).

Applicants respond that neither Melief nor any of the other cited references teach all of the limitations of the present invention because they do not teach or suggest the claimed anti-CD40 antibodies of the invention, which agonize CD40 and are able to block the binding of CD40 to CD40L by 16-88%. None of the cited references have these limitations, and it would not be obvious to generate or search for an antibody that activates CD40 and also blocks CD40:CD40L binding within the specified percent range.

As argued above, Applicants respectfully submit that Melief does not disclose agonist antibodies directed against human CD40 that block binding of CD40 to CD40L by 16-88%. Similarly, none of the additional references cited teach or suggest such antibodies. The remaining references (Zhou, Caux, Katira, Schwabe, and Maraskovsky) fail to provide the missing limitations, and provide no suggestion or motivation to combine with Melief, or any other reference, to generate such antibodies. The Examiner has failed to satisfy all three prongs of the test outlined above, and accordingly, has not established a *prima facie* case of obviousness.

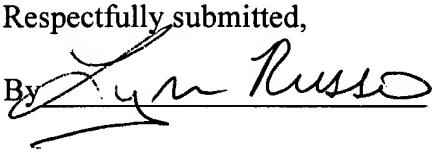
In view of the foregoing, Applicants respectfully submit that all claims as herein presented are non-obvious. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: October 12, 2005

Respectfully submitted,

By 

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BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Tanox, Inc.
Attn: Eric Mirabel
10301 Steller Link
Houston, TX 77025

Deposited on Behalf of: Tanox, Inc.

Identification Reference by Depositor:	**Patent Deposit Designation**
Hybridoma: MAb 186-21-1	PTA-2993
Hybridoma: MAb 186-64-1	PTA-2994
Hybridoma: MAb 186-70-3	PTA-2995
Hybridoma: MAb 186-4-1	PTA-2996
Hybridoma: MAb 186-7-2	PTA-2997
Hybridoma: MAb 186-15-1	PTA-2998
Hybridoma: MAb 186-26-3	PTA-2999

(Ref: Docket or Case No.: 00-03)

The deposits were accompanied by: __ a scientific description _ a proposed taxonomic description indicated above. The deposits were received January 31, 2001 by this International Depository Authority and have been accepted.

AT YOUR REQUEST: X We will inform you of requests for the strains for 30 years.

The strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strains.

If the cultures should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace them with living cultures of the same.

The strains will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the cultures cited above was tested February 9, 2001. On that date, the cultures were viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:

Tanya Nunnally, Patent Specialist, Patent Depository

Date: February 13, 2001

BP4/9

AXXORA

Apoptosis

For Pricing Information click here and submit your country.

ALX-805-046 [ALEXIS] Revised 10-May-05

Monoclonal Antibody to CD40 (mouse) (FGK45)

SYNONYMS	anti-TNFRSF 5 (mouse) MAb (FGK45)
PRODUCT LINE	Apoptosis
PRODUCT FAMILIES	CD40/CD40L [CD154]

Ordering Information

Product Numbers	Format	Size	Unit Price	Quantity
ALX-805-046-C100		100 µg		
ALX-805-046-C500		500 µg		
ALX-805-046B-C050	Biotin	50 µg		

Product Specification

ORIGINAL MANUFACTURER	ALEXIS Biochemicals
SPECIES CROSSREACTIVITY:	Mouse
CLONE:	FGK45
ISOTYPE:	Rat IgG2a
CONCENTRATION:	FGK45: 1mg/ml FGK45-Biotin: 0.5mg/ml
FORMULATION:	Liquid. Protein G-affinity purified antibody in sterile PBS.
IMMUNOGEN:	Recombinant mouse CD40 fusion protein.
SPECIFICITY:	Recognizes mouse CD40.
APPLICATION:	Flow Cytometry Functional Application (activates B and NK cells *in vivo* and *in vitro*)
FUNCTIONAL APPLICATION:	FC Others Others FUNC: Activates B and NK cells *in vivo* and *in vitro*.
SHIPPING:	SHIPPED ON BLUE ICE
SHORT TERM STORAGE:	+4°C
USE/STABILITY:	FGK45: Long Term Storage: -20°C FGK45-Biotin: Long Term Storage: +4°C.
HANDLING:	Avoid freeze/thaw cycles.

Product Description

Widely used stimulatory MAb to CD40 [1,2]. Shown to indirectly activate natural killer (NK) cells, producing significant antitumor and antimetastatic effects [3]. Effective in boosting immune responses against infectious agents and can potentially be used to treat chronic autoimmune inflammatory processes [4].

Product Specific Literature References

[1] *The SCID but not the RAG-2 gene product is required for S mu-S epsilon heavy chain class switching:* A. Rolink, et al.; Immunity **5**, 319 (1996) Abstract
[2] *Characterization of immature B cells by a novel monoclonal antibody, by turnover and by mitogen reactivity:* A.G. Rolink, et al.; Eur. J. Immunol. **28**, 3738 (1998) Abstract
[3] *Anti-CD40 antibody induces antitumor and antimetastatic effects: the role of NK cells:* J.G. Turner, et al.; J. Immunol. **166**, 89 (2001) Abstract
[4] *Therapeutic activity of agonistic monoclonal antibodies against CD40 in a chronic autoimmune inflammatory process:* C. Mauri, et al.; Nat. Med. **6**, 673 (2000) Abstract
Click here for a complete literature overview:

RELATED PRODUCT GROUPS
Apoptosis > TNF-R Superfamily Antibodies / Antibodies > Monoclonal Antibodies